REMARKS/ARGUMENTS

The Present Invention

The present invention is directed to a method of treating cancer, a method of treating an immune-related disease, a method of preventing a cancer in a mammal, a pharmaceutical composition, a method for inducing apoptosis of a natural killer (NK) cell, and a method of activating NK cell cytolytic activity.

The Pending Claims

Claims 1-5, 8, 11-22, 25, 28-30, 58-63, 66, and 67 are pending of which claims 1-5, 8, 11-22, 25, 28-30, 58, and 60-63 are withdrawn, and claims 66 and 67 are newly added.

The Office Action

The Office Action conveys that References AI-AM have not been considered, since their publication dates were not indicated on the Form 1449 of the Information Disclosure Statement (IDS) submitted on September 24, 2004. The Office Action objects to the specification for allegedly not having trademarks and nucleotide and amino acid sequences properly labeled. The Office Action objects to claim 59 as allegedly depending on a claim directed to a non-elected invention. The Office Action rejects claim 59 under 35 U.S.C. 112, second paragraph, as allegedly indefinite, and under Section 112, first paragraph, as allegedly failing to meet the written description requirement. The Office Action states that claims 1-15 and 48-51 are rejected under 35 U.S.C. 112, first paragraph, as allegedly lacking enablement. However, per the telephonic interview of July 3, 2007, with Examiner Duffy, the recitation of "claims 1-15 and 48-51" was a typographical error and only claim 59 is, in fact, rejected. Reconsideration of the objections and rejections is hereby requested.

The Notice to Comply

The Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures indiates that the application fails to comply with the requirements of 37 C.F.R. 1.821-1.825, since the specification at, for example, paragraph [0003] contains the amino acid sequence "WSXWS" which is not labeled with a sequence identification number corresponding to a sequence listing. In response, the

specification has been amended to label all sequences with a sequence identification number which corresponds to the sequence listing submitted herewith. The sequence listing is the same as the one submitted on September 24, 2004, except that the one submitted herewith includes the amino acid sequence WSXWS, and the sequences of GenBank Accession Nos. AAG29348, AF254069, AAG29349, and AF254070, which sequences were incorporated by reference.

The Amendments to the Specification and Claims

The specification has been amended to include an incorporation-by-reference of material submitted electronically. Also, as discussed above, the specification has been amended to label all nucleotide and amino acid sequences pursuant to 37 C.F.R. 1.821. Futher, the specification has been amended to label all trademarks pursuant to 37 C.F.R. 1.71. Claims 31-38 and 57 have been cancelled. Claim 59 has been amended to an independent format, to recite "polynucleotide encoding SEQ ID NO: 6 or 8," and to delete references to variants and fragments of IL-21. Claims 66 and 67 have been added and are supported by the specification at, for example, paragraphs [0026] and [0029]. No new matter has been added by way of these amendments.

Discussion of the Information Disclosure Statement

The Office Action conveys that References AI to AM, all of which are GenBank Accession Records, have not been considered, because the publication dates of the references are not indicated on the Form 1449 submitted with the IDS of September 24, 2004. In response, Applicants submit herewith a supplemental IDS with Form 1449 indicating the public release dates of References AI to AM, which are now listed as References AX-BA. Applicants accordingly request the consideration of these references in connection with the instant application.

Discussion of the Objection to the Specification

The Office Action objects to the specification for allegedly not having all nucleotide and amino acid sequences labeled with an appropriate sequence identifier and for allegedly not having all trademarks appropriately labeled. The specification has been amended herein to comply with 37 C.F.R. 1.821 and 1.71. Specifically, all nucleotide sequences of 10 or

more nucleotides and all amino acid sequences of 4 or more amino acids have been properly labeled with a sequence identifier which corresponds with the sequence listing submitted herewith. Also, all trademarks have been properly labeled. In view of the amendments to the specification, the objection to the specification should be withdrawn.

Discussion of the Objection to the Claim

The Office Action objects to claim 59 as allegedly depending on a claim directed to a non-elected invention. Claim 59 has been amended into independent format. Thus, the objection is moot.

Discussion of the Indefiniteness Rejection

The Office Action rejects claim 59 as allegedly indefinite. Specifically, the Office Action argues that the term "IL-21" which is used as the sole means for identifying the polynucleotide referred to in the claims is improper. Claim 59 has been amended to delete reference to IL-21 and instead recites "a polynucleotide encoding SEQ ID NO: 6 or 8." Thus, the rejection is moot.

Discussion of the Written Description Rejection

Claim 59 is rejected as allegedly lacking written description. Specifically, the Office Action argues that the specification describes the structure of only one polynucleotide that induces apoptosis of NK cells, yet the claim encompasses a large genus of polynucleotides encoding an IL-21 polypeptide, variant, or fragment thereof. The Office Action concludes that the specification does not describe a representative number of species for the genus of polynucleotides of claim 59. This rejection is traversed for the reasons set forth below.

As a first matter, claim 59 has been amended to recite "a polynucleotide encoding SEQ ID NO: 6 or 8." SEQ ID NO: 6 is the amino acid sequence of the human IL-21 protein, while SEQ ID NO: 8 is the amino acid sequence of the mouse IL-21 protein. The claim also has been amended to delete reference to a variant or fragment of an IL-21 polypeptide. Therefore, the size of the genus of polynucleotides and the scope of the claim have been amended.

Further, the specification describes the amino acid and nucleotide sequences of the mouse and human IL-21 gene by way of providing and incorporating by reference GenBank Accession Record Nos. AAG29348, AF254069, AAG29349, and AF254070. See paragraph [0021] beginning on page 5. Accordingly, at least two species of the genus of polynucleotides of the claim is described by the specification.

Furthermore, an amino acid sequence supports the entire genus of DNA sequences that can encode the amino acid sequence because the state of the art has developed such that is it a routine matter to convert one to the other. *In re Wallach,* 3778 F.3d 1330, 1333-1334, 71 USPQ2d 1939, 1942 (Fed. Cir. 2004). In the instant case, since the amino acid sequences of the mouse and human IL-21 proteins are provided by the specification, as discussed above, a genus of polypeptides encoding either the mouse or human IL-21 protein (i.e., either SEQ ID NO: 6 or 8) is supported by the instant specification.

It appears that the Office Action requires that the structure of each and every species of the genus is set forth in the specification, even though the amino acid and nucleotide sequences of IL-21 were known in the art. Applicants remind the Office that, when the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh. *Capon v. Eshhar*, 418 F.3d 1349, 1358, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005).

According to the Office Action, the specification does not adequately support the genus of polynucleotides encoding a variant or fragment of an IL-21 polypeptide. Claims 66 and 67 have been added. Claim 66, which is directed to a method of inducing apoptosis of a NK cell, comprising contacting the NK cell with a polynucleotide encoding a variant of SEQ ID NO: 6 or 8, wherein the variant has an amino acid sequence that is greater than 95% identical to the amino acid sequence of SEQ ID NO: 6 or 8, is supported by the specification at, for example, paragraph [0029]. Claim 67, which is directed to a method of inducing apoptosis of a NK cell, comprising contacting the NK cell with a polynucleotide encoding a fragment of about 5 to about 30 amino acids of SEQ ID NO: 6 or 8, wherein the fragment retains the biological activity of SEQ ID NO: 6 or 8, is supported by the specification at, for example, paragraph [0026]. Given their structural and functional features, one of ordinary

skill in the art can immediately envision such variants and fragments of IL-21, such that the genus of polynucleotides encoding them are adequately described by the instant specification.

In view of the foregoing, the instantly pending claims meet the written description requirement of Section 112, first paragraph. Applicants therefore request that the rejection be withdrawn.

Discussion of the Enablement Rejection

Claim 59 is rejected as allegedly lacking enablement. Specifically, the Office Action argues that claim 59 encompasses a method of administering *in vivo* an IL-21 gene to humans, thereby encompassing gene therapy. The Office Action argues that, because the art of gene therapy is problematic, unpredictable, and still in its infancy, the claimed methods require undue experimentation. The Office Action also argues that, although a method of inducing apoptosis of a murine NK cell comprising the use of a polynucleotide encoding a murine IL-21 is enabled, a method of inducing apoptosis of human NK cells using a polynucleotide encoding a human IL-21 is non-enabled. According to the Office Action, there are fundamental differences between murine and human NK cells, such that it is highly unpredictable as to whether the method would function in the context of human NK cells. The rejection is traversed for the reasons set forth below.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent may be enabling even though some experimentation is necessary; the amount of experimentation, however, must not be unduly extensive. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

In the instant case, the nature of the invention is a method of inducing apoptosis of a natural killer (NK) cell comprising contacting the NK cells with a polynucleotide encoding (i) SEQ ID NO: 6 or 8, (ii) a variant of SEQ ID NO: 6 or 8, wherein the variant has an amino acid sequence that is greater than 95% identical to the amino acid sequence of SEQ ID NO: 6 or 8, or (iii) a fragment of about 5 to about 30 amino acids of SEQ ID NO: 6 or 8, wherein the fragment retains the biological activity of SEQ ID NO: 6 or 8, in an amount effective to induce apoptosis of the NK cell. The breadth of the claim is limited to the use of the polynucleotides encoding SEQ ID NO: 6 or 8, or a variant or fragment thereof, as described above, and to amounts of the polynucleotides effective to induce apoptosis of the NK cell. The claimed method could take place *in vitro* or *in vivo* and the NK cells of the claimed method are not limited to any particular type of NK cells.

The instant specification provides ample amounts of direction and guidance for practicing the inventive method and further provides working examples. For instance, the specification at, for instance, paragraphs [0091] through [0096] demonstrates the cloning of both human and murine IL-21 polynucleotides. The specification at, for example, paragraphs [00100] through [00105] demonstrates a method of administering to a mammal an IL-21 polynucleotide. Further, the specification at, for instance, Figure 6A and paragraph [00132] demonstrate that administration of a plasmid comprising an IL-21 polynucleotide cloned from cells using the primers of SEQ ID NOs: 3 and 4 causes NK cells of a mouse to apoptose *in vivo*.

The Office argues that the art of gene therapy is still in its infancy, is highly unpredictable and its successful application has been hindered by numerous limitations. The Office Action further contends that the state of the art, as a whole, is well defined by Pandha et al., *Current Opinion in Invest. Drugs* 1: 122-134 (2000), which states that the limitations of gene therapy include low efficiency of gene transfer, poor specificity or response and methods to accurately evaluate responses, and lack of truly tumor-specific targets at which to aim. The Office Action concludes that, because the claimed method encompasses gene therapy, the claimed method is non-enabled.

In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*,

999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by the claim is not adequately enabled by the disclosure). MPEP 2164.04 (emphasis added) In the instant case, the Office Action argues based on general teachings on gene therapy. Since the argument is not specific to the claimed invention, it is not a sufficient basis for an enablement rejection.

The Office Action further argues gene therapy using retroviral is so dangerous that the Department of Health and Human Services (DHHS) has released a memorandum that urges investigations involving retroviral transduction-based gene therapy to be discontinued. However, as evidenced by Morgan et al., *Science* 314: 126-129 (e-publication on August 31, 2006), laboratories of the National Institutes of Health, which is a part of the DHHS, have continued research on retroviral transduction-based gene therapy.

Moreover, the Office Action argues that the specification at Figure 1 teaches that more than 2/3 of the expression of murine IL-21 is lost after 3 days. Since the specification demonstrates that apoptosis of NK cells was accomplished *in vivo* (Example 7), the alleged loss of expression is immaterial to the enablement of the claimed invention.

On another note, the Office Action cites to Parrish-Novak et al., *J. Leukocyte Biol.* 72: 856-863 (2002) as a basis for its argument that there are fundamental differences between the behavior of IL-21 in mouse cells as compared to that in human cells. The Office Action concludes that it is highly unpredictable whether a human IL-21 polynucleotide would induce apoptosis in human NK cells. However, Parrish-Novak et al. additionally states that "[the] activity of IL-21 on murine and human NK cells in fact may be similar when dose, stage of maturation, and activiation state are matched" (last sentence of last paragraph of right hand column on page 861). Therefore, even the reference that the Office Action relies upon speculates that the behavior of IL-21 in mouse and humans is likely to be similar, such that one could reasonably predict what would occur in a human based on mouse model data.

Further, as stated in the Declaration under 37 C.F.R. 1.132 of Dr. Warren Leonard, which is submitted herewith, mouse models are predictive of the biological activity of a molecule in a human context, such that he believes that a polynucleotide encoding human IL-21 would likely induce apoptosis in human cells, based on the mouse model data provided in the instant application.

In view of the foregoing, claim 59, as well as claims 66 and 67, are in fact enabled. Applicants therefore request the withdrawal of the rejection.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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